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In re Patent Application of HANNA et al. Group Art Unit: 1644

Application Serial No. 09/435,992 Examiner: Phillip Gambel

Filed: November 8, 1999

Title: TREATMENT OF B CELL MALIGNANCIES USING ANTI-CD40L ANTIBODIES IN COMBINATION WITH ANTI-CD20 ANTIBODIES AND/OR CHEMOTHERAPEUTICS AND RADIOTHERAPY

* * * * *

AMENDMENT AND REPLY

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Final Office Action dated July 10, 2002, please enter and consider the following amendments and remarks.

Do not enter 3/7/03 RC

Withdrawal of Finality is Requested:

The Applicants respectfully request withdrawal of finality of the office action dated July 10, 2002, on the grounds that the species of claimed invention that has been examined is different from the species that was elected for examination by the Applicants.

Entered via RCE #30

The Prior Office Actions are Not Directed to the Elected Invention:

The Applicants strongly traverse and protest the Examiner's arbitrary decision in the two Office Actions to treat the elected invention as a method employing the combination of an anti-CD40L antibody that is non-labeled and an anti-CD20 antibody that is radiolabeled. Neither the first Requirement for Restriction mailed March 15, 2001, nor the second Requirement to Elect Species mailed July 3, 2001, clearly stated a requirement that the Applicants must elect between a method that uses an anti-CD20 antibody that is non-radiolabeled and a method that uses a radiolabeled anti-CD20 antibody.

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The Requirement for Restriction mailed March 15, 2001, called for election between:

Group I: claims 1-41, drawn to methods for treating B cell malignancies with anti-CD40L antibodies alone or in combination with other antibodies specific for CD20 or CD40, or in combination with chemotherapeutic agents;

and

Group II: claims 42-56, drawn to compositions of anti-CD40L antibodies and other antibodies or chemotherapeutic agents.

The Requirement for Restriction further stated that claims 1 is generic, and that if Group I was elected, the Applicants must also elect for examination a method that employs one of the following five patentably distinct species:

A) anti-CD40L antibody;
B) anti-CD40L antibody and a second antibody (e.g., anti-CD20 antibody);
C) anti-CD40L antibody and a chemotherapeutic agent;
D) anti-CD40L antibody and radiotherapy;
E) combinations of anti-CD40L antibody with a second antibody, chemotherapeutic agent, or radiotherapy.

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In response to the Requirement for Restriction, the Applicants filed a letter on April 16, 2001, in which they elected without traverse the invention of Group I, claims 1-41, and further elected Species B, which they further limited to the use of an anti-CD40L antibody and an anti-CD20 antibody. The Applicants also stated that they assumed that the election requirement "is only for purposes of examination, and that the Examiner will extend the search to other species upon a determination that the elected combination is patentable," and that "[a]t the very least, the search should be extended to use of anti-CD40L antibody alone for treatment of lymphoma as this is overlapping with the elected species."

Following entry of the Applicants Election mailed April 16, 2001, another Requirement to Elect Species was mailed by the U.S. Patent and Trademark Office on July 3, 2001. The second Requirement to Elect Species acknowledged the Applicants election of Group I, Species B; and "for clarity," it "invited" the Applicants to elect either anti-CD40L

alone, or the combination of an anti-CD40L antibody and an anti-CD20 antibody. The second Requirement to Elect Species also "invited" the Applicants to indicate that the use of art known chemotherapeutics and radiotherapy were obvious in treating CD40+ malignancies, particularly B cell lymphomas and B cell leukemias," and then stated that "[t]herefore, applicants' election of either anti-CD40L alone or the combination of an anti-CD40L antibody and an anti-CD20 antibody would be considered in combination with the art known use of chemotherapeutics and radiotherapy were obvious in treating B cell lymphomas and B cell leukemias." The second Requirement to Elect Species further "invited" the Applicants "to indicate that the plurality of species set forth in claims 13-19 and 36-41, as they read on radiolabels and chemotherapeutics were obvious variants in the treatment of B cell lymphomas and leukemias at the time the invention was made;" or else, to elect a species for radiolabels and chemotherapeutics. The Requirement to Elect Species stated that the claimed chemotherapeutics are patentably distinct, because their structures and modes of action are different, and that the Applicants should submit or identify evidence to the contrary if they choose to traverse that the claimed chemotherapeutics are patentably distinct.

The second Requirement to Elect Species then set out an additional requirement for election of species, in the statements quoted below:

"3. Upon reconsideration and for clarity, the following election species is set forth.

Claims 1-41 are generic to a plurality of disclosed patentably distinct species comprising .(sic) Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though the requirement is traversed.

This application contains claims directed to the following patentably distinct species of the claimed Group I: wherein the CD40+ malignancy is:

A) a B cell lymphoma or

B) a B cell leukemia."

The second Requirement to Elect Species further stated that if B cell lymphoma is elected, the Applicants must further elect between methods wherein the B cell lymphoma is A) Hodgkin's Disease, and B) Non-Hodgkin's Disease; and it stated that the species are patentably distinct because the pathological conditions differ in etiologies and therapeutic endpoints.

In their reply to the second Requirement to Elect Species, mailed September 4, 2001, the Applicants confirmed their election of Group I, species B (use of an anti-CD40L antibody and an anti-CD20 antibody), and in a good faith effort to respond to the additional requirement to elect a species, they further elected:

(a) leukemia as the CD40+ malignancy,

(b) ^{90}Y as the radiolabel, and

(c) alkylating agents as the chemotherapeutics,

to be searched in common with the elected species. The applicants also submitted new claims 57-59 that recite limitations within the elected species.

Instead of examining the elected invention, which comprises administering unlabeled anti-CD40L antibodies in combination with unlabeled anti-CD20 antibodies to treat a B cell leukemia, the initial Office Actions mailed November 21, 2001, and the Final Office Action mailed July 10, 2002, both arbitrarily state that:

> "For the purposes of this Office Action, the anti-CD20 antibody is radiolabeled (e.g., ^{90}Y) and anti-CD40L antibody is not radiolabeled," (see page 2).

The Office Actions supported this arbitrary, examiner-imposed election with the statement that:

> "This election of an anti-CD20 antibody which is radiolabeled (e.g., ^{90}Y) and an anti-CD40L antibody which is not radiolabeled appears consistent with the Examples set forth in the instant specification and the election of leukemias rather than lymphomas," (see page 2).

The latter statement apparently ignores the fact that all of the examples disclosed in the present application that describe using antibodies to kill lymphoma and leukemia cells describe methods that use non-radiolabeled anti-CD40L and anti-CD20 antibodies.

The rule for Requirement for restriction stated in 37 C.F.R. § 1.142 (a) is that if two or more independent and distinct inventions are claimed in a single application, the examiner in an Office action will require **the applicant** to elect an invention to which the claims will be restricted. Likewise, the rule for Election of species stated in 37 C.F.R. § 1.146 is that in an

application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, it is **the applicant** who must elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable (emphasis added). It is therefore contrary to the rules for Restriction and Election stated in 37 C.F.R. §§ 1.142 (a) and 1.146 for an examiner to arbitrarily identify and elect a species of the invention to be examined without the Applicants' concurrence. It is, after all, the Applicants' invention, and it is the Applicants that pay the fee to the U.S.P.T.O. to have their invention examined.

In the present application, the Applicants fully complied with the Requirement for Restriction mailed March 15, 2001, by electing Group I, species B. Dependent claims 11 and 12 of elected Group I specify a method wherein one or both of the anti-CD40L and anti-CD20 antibodies are radiolabeled. Accordingly, the claims of elected Group I, species B, clearly include in their scope both radiolabeled and non-radiolabeled antibodies. The Applicants also complied with the Requirement for Election mailed July 3, 2001, by electing leukemia as the disease, ^{90}Y as the radiolabel, and alkylating agents as the chemotherapeutics. Nothing in their reply to the Requirement for Election mailed July 3, 2001, or to the Requirement for Restriction mailed March 15, 2001, indicates a desire by the Applicants to elect an invention limited to a method that uses non-radiolabeled anti-CD40L antibodies and radiolabeled anti-CD20 antibodies. The Applicants reasonably intended that the elected claims be examined in their full scope; i.e., that the claims be interpreted as including methods wherein none, one, or both of the anti-CD40L and anti-CD20 antibodies are radiolabeled. This intention is fully in accord with the disclosed examples, which describe methods for promoting cytotoxicity of lymphoma and leukemia cells using non-radiolabeled anti-CD40L and anti-CD20 antibodies (see Examples 2-4).

Neither the Requirement for Restriction mailed March 15, 2001, nor the Requirement for Election mailed July 3, 2001, stated a requirement that the Applicant must elect whether the anti-CD40L and anti-CD20 antibodies of Group I, species B, are radiolabeled or non-radiolabeled. The Office Actions mailed November 21, 2001, and July 10, 2002, ignored the Applicants' elections in their responses in their responses to the Requirement for Restriction mailed March 15, 2001, and the Requirement for Election mailed July 3, 2001, and imposed an election of a method limited to using non-radiolabeled anti-CD40L antibody and radiolabeled anti-CD20 antibody without the Applicants' concurrence.

Both Office Actions then proceeded to reject the claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to recite radiolabeled anti-CD20 antibody as "the elected invention;" and to reject the claims under 35 U.S.C. 103(a) as being obvious in view of references that describe the use of radiolabeled anti-CD20 antibodies for treating B cell malignancies. In order to have cytotoxic effect against neoplastic cells, radiolabeled antibodies only need to bind to the targeted cancer cells - when the radiolabel decays, it inflicts damage on the bound cells. Primary requisites for obtaining cytotoxic activity using radiolabeled antibodies are that the radiolabeled antibodies binds specifically and with high affinity to a surface antigen of the neoplastic cells, and that the method of administration is one that results in delivery and binding of the radiolabeled antibodies to the targeted cells. In contrast, the invention elected by the Applicants encompasses using non-radiolabeled antibodies. Whether or not such non-radiolabeled antibodies have anti-neoplastic activity against leukemia cells depends on the metabolic response of the target cells and cooperative responses of effector cells to the binding of the antibodies to the targeted surface antigen. The factors that determine the expectation of success of the elected method that uses non-radiolabeled antibodies factors are therefore significantly different than the factors that are at issue in establishing a prima facie case of obviousness of a method using radiolabeled antibodies.

Pursuant to 37 C.F.R. §§ 1.142 and 1.146, which entitle the applicant to elect the group and species of invention to be examined, the Applicants respectfully traverse and request reconsideration of the examiner-imposed election of a method using non-radiolabeled anti-CD40L antibody and radiolabeled anti-CD20 antibody, as this election is different from the Applicants' election. Since the Examiner has persisted in imposing the improper election in both the initial and Final Office Actions, the Applicants also respectfully request that the Finality of the Office Action mailed July 10, 2002 be withdrawn, and that a new Office Action be prepared that is directed to the invention Group and Species elected in response to the Requirement for Restriction mailed March 15, 2001, and the Requirement for Election mailed July 3, 2001, as set forth in the amended claims submitted herewith.

Regarding the Public Availability of Humanized MAb 24-31 (IDEC-131) and IDEC-C2B8 (RITUXAN®):

The claims recite a method for treating leukemia comprising administering a therapeutically effective amount of an anti-CD20 antibody identified in the specification by the designations IDEC-C2B8 and Rituxan®; and also administering a therapeutically effective amount of an anti-CD40L antibody described in the specification as IDEC-131 and as humanized MAb 24-31.

To comply with the enablement requirements of 35 USC 112, 1st paragraph, the disclosed an anti-CD20 and anti-CD40L antibodies must be known and readily available to the public, or obtainable by a repeatable method set forth in the specification.

A method for making the chimeric anti-CD20 antibody identified as IDEC-C2B8 is described in U.S. Patent No. 5,843,439, ("the '439 patent") which is incorporated into the present application by reference in its entirety. The '439 patent discloses the DNA expression vector TCAE 8 that comprises a first expression cassette containing a DNA sequence encoding a human kappa light chain constant region, and a second expression cassette containing a DNA sequence encoding a human gamma 1 heavy chain constant region (see Figure 1). The nucleotide sequence of vector TCAE 8 is disclosed in Figures 2A-2F of the '439 patent. As described in the '439 patent (see columns 20-21), IDEC-C2B8 was made by cloning DNA molecules encoding the variable regions of the light and heavy chains of the murine anti-CD20 antibody 2B8, and inserting these into sites in the TCAE 8 vector adjacent to the DNA sequences encoding, respectively, the human kappa light chain constant region and the human gamma 1 heavy chain constant region. Figures 3A-F disclose the nucleotide sequences of the DNA encoding the chimeric light and heavy chains of IDEC-C2B8 produced as described in the '439 patent. The disclosure in the '439 patent of the nucleotide sequences of the chimeric light and heavy chains of IDEC-C2B8, and the map and nucleotide sequence of vector TCAE 8, enables persons skilled in the art to make functional IDEC-C2B8 without undue experimentation. Therefore, deposit of cells that make IDEC-C2B8 is not required to comply with the enablement requirements of 35 USC 112, 1st paragraph, with respect to the claimed IDEC-C2B8 anti-CD20 antibodies.

A method for making the chimeric anti-CD40L antibody identified as IDEC-131 is described in U.S. Patent No. 6,001,358 ("the '358 patent"), which is incorporated into the present application by reference in its entirety. The '358 patent discloses a DNA expression

vector that comprises a first expression cassette containing a DNA sequence encoding a human kappa light chain constant region and the variable region of the light chain of murine 24-31 antibody, and a second expression cassette containing a DNA sequence encoding a human gamma 1 heavy chain constant region and the variable region of the heavy chain of murine 24-31 antibody (see Figure 1).

The '358 patent (see Examples 7-9, columns 25-27) describes making IDEC-131 by cloning DNA molecules encoding the variable regions of the light and heavy chains of the murine anti-CD40L antibody 24-31, and inserting these into a vector comprising DNA sequences encoding, respectively, the human kappa light chain constant region and the human gamma 1 heavy chain constant region. The amino acid and nucleotide sequences of the human and murine antibody segments that comprise the humanized 24-31 antibody that is IDEC-131 are disclosed in Figures 4-8 of the '358 patent. The disclosure in the '358 patent of the nucleotide sequences of the chimeric light and heavy chains of IDEC-131, and the description of a reproducible method by which the antibodies can be made, enables persons skilled in the art to make functional IDEC-131 without undue experimentation. Therefore, deposit of cells that make IDEC-131 is not required to comply with the enablement requirements of 35 USC 112, 1st paragraph, with respect to the claimed humanized 24-31 anti-CD40L antibodies.

Request for Entry of Figures Representing the Results Described in the Specification:

The Applicants respectfully request entry of Figures 1-4 submitted with Applicants' letter of April 22, 2002. As discussed with the Examiner in the earlier telephone conference regarding the Figures, the figures contain data that corresponds to experiments described in the examples, and the subject matter of the figures is described in the application. The Applicants have also provided an affidavit by one of the inventors, Hari Hariharan, who attests to the fact that these figures are the same figures described in the as-filed application.

Applicants' request for entry of the figures was forwarded to the Office of Petitions of the U.S. Patent and Trademark Office, and was there dismissed, with the direction that the Petitioners should submit an amendment requesting entry of the six sheets of drawings, as the authority to decide whether to enter the figures rests with the Examiner. The figures may be entered provided that they do not contain new matter. Accordingly, the Applicants respectfully request amendment of the specification by entry of Figures 1, 2a, 2b, 3a, 3b, and 4, as indicated below: